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EXAMINER	
GARVEY, TARA L	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 07/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/877,406	HANDELSMAN ET AL.	
	Examiner	Art Unit	
	Tara L Garvey	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *April 19,2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) *1,31 and 34-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-30,32,33 and 41-45* is/are rejected.

7)☒ Claim(s) *2,6,7,10-15,19,25,26,30 and 42-44* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/24/01 & 4/22/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I in the reply filed on April 19, 2004 is acknowledged. The traversal is on the ground(s) that the subject matter is inextricably linked and a search for the elected claims will find material for the other claims. This is not found persuasive because the inventions are in different classes and subclasses. While the searches may partially overlap, they also extend beyond one another. A reference could anticipate one group and not another. In, for example, the case of a product and a process of making that product, a reference may exist that teaches the product of Group III drawn to pharmaceutical compounds produced by recombinant organisms, but does not teach the method of making this product as claimed in Group I. Therefore, the searches for these two groups are distinct.

The requirement is still deemed proper and is therefore made FINAL.

Claims 34-39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on April 19, 2004.

Claim Objections

Claims 6 and 7 are objected to because of the following informalities: The use of [[-5]] is not understood and should be removed. Appropriate correction is required.

Claim 14 is objected to because of the following informalities: The word "low" is repeated in line two of the claim. Appropriate correction is required.

Claim 12 is objected to because of the following informalities: The word "of" is missing after consisting on line 2. Appropriate correction is required.

Claims 25 and 30 are objected to because of the following informalities: The word "induces" is grammatically incorrect and should be "induce". Appropriate correction is required.

Claim 26 is objected to because of the following informalities: The word "or" is needed between the last two words on line 3 of the claim. Appropriate correction is required.

Claim 45 is objected to because of the following informalities: The use of [[2C]] is not understood and should be removed. Appropriate correction is required.

Claims 2, 10, 11, 12, 13, 14, 15, 42, 43 and 44 objected to because of the following informalities: The spelling of 'microrganism" is incorrect and should be spelled microorganism. The spelling of "anerobes" in claim 15 is incorrect and should be anaerobes. Appropriate correction is required.

Claim 19 is objected to because of the following informalities: The spelling of "Agribacterium" in line 3 of the claim is incorrect and should be spelled Agrobacterium. Appropriate correction is required.

Claims 14 and 15 refer to prokaryotes and anaerobes, respectively. While this terminology is correct, Applicant may wish to use "prokaryotic cells" and "anaerobic

cells" instead, to be consistent with claims 10 and 11. Alternatively, claims 10 and 11 could be amended to be consistent with claims 14 and 15.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2 and 33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 2 is drawn to a method of using host cells containing a vector expressing genomic DNA from uncultivated microorgansims to detect a compound produced by the host cells. Claim 33 is drawn to the method of claim 2 in which a pharmaceutical composition of compounds produced by the host cell is formulated. The specification does not describe the method for the formulation of a pharmaceutical composition or the chemical structure and/or function of the compounds that are a part of the composition. Therefore, the applicant does not provide evidence of possession of the composition.

The specification describes isolation of genomic DNA from environmental samples containing uncultivated microorganisms, construction of expression vectors

containing the genomic DNA from various microorganisms, transformation of a host cell with the vectors and maintenance of the host cells under conditions to express the DNA. The prior art does not offset the lack of description in the specification in that it does not describe potential drugs with specific properties and uses that would be discovered and produced using the methods described in the invention. Therefore, there is not a structural and functional basis provided by the prior art or the specification for one of skill in the art to envision pharmaceutical compositions containing compounds that are yet to be discovered.

Claim 2-30, 32 and 33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for producing host cells expressing genomic DNA from uncultivated microorganisms, does not reasonably provide enablement for detecting a compound without prior knowledge of that compound or the nature of that compound. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art, relative skill in the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claim, with the most relevant discussed below.

Nature of the invention: The rejected claims are drawn to a method of identifying a compound produced by a biosynthetic pathway by using host cells containing a vector that express genomic DNA isolated from uncultivated microorganisms and detecting a compound produced by the host cells. The method involves isolating genomic DNA from uncultivated microorganisms, cloning the genomic DNA into an expression vector and transforming the vector into a host cell. The host cells are maintained under conditions in which they will express the genomic DNA contained within them and compounds produced by these host cells will be detected. Thousands of clones will be produced by this method and the clones producing the detected compounds will need to be identified.

Breadth of the claim: The claims are extremely broad in that they encompass detection of any compound that may be produced by the host cells expressing the genomic DNA of the uncultivated microorganisms. The different types of potential compounds that could be detected is extensive since the host cells are to contain vectors expressing the genomic DNA from at least ten different microorganisms. In addition, the enormous amount of clones produced will need to be screened to determine which clone is producing the detected compound.

Guidance in the specification/Existence of a working example: The specification describes how to construct the host cells expressing the isolated genomic DNA from many uncultivated microorganisms and mentions possible detection techniques. It does not describe how to approach the detection of all the possible compounds produced by

such a method when one does not have knowledge of the nature of the compounds produced.

State of the art: At the time of the applicants' invention, the use of replicable vectors to express genomic DNA isolated from uncultivated microorganisms of an environmental sample in a host cell was known. Maintaining the host cells under conditions in which novel compounds from biosynthetic pathways would be expressed was also known in the art (Short et al US 6,057,103 and Thompson et al US 5,824,485). The prior art teaches detecting compounds expressed by the host cells, but describes analyzing the cells for various bioactivities. The prior art does not describe how to approach a situation in which one is to perform an analysis for an unknown compound in which one does not know its function or physical properties.

Predictability of the art: The ability of microorganisms to produce detectable compounds as well as the use of recombinant techniques to tap into the vast resource of uncultivated microorganisms to find novel compounds was known at the time of the invention. One is unable to predict which portions of the genomes will be cloned into the vectors, which microorganisms will be represented in the host cells and what will be the nature of all the compounds produced in this situation. Therefore, the experimentation to find a new compound with unknown properties would result in a large amount of trial and error and may result in a potential compound being overlooked.

Quantity of experimentation: In order to practice the claimed invention, one of ordinary skill in the art would have to envision the characteristics of all the possible

classes of novel compounds that would be produced by at least ten different uncultivated microorganisms in order to determine the methods needed to detect them. First, the amount of planning that would have to go into determining what to analyze would be extremely time consuming. Second, the screening of the host cells and then determining from millions of clones which ones express the compound for an undisclosed number of methods to detect a compound of any type creates extensive experimentation.

In view of the unpredictable nature of the art, the lack of direction in the specification and the enormous amount of experimentation needed to detect unknown compounds, the experimentation would have been undue. Thus, it would require undue and unpredictable experimentation for one of skill in the art to perform the claimed invention. Therefore, the claimed invention of detecting compound produced by host cells containing vectors expressing genomic DNA from many uncultivated microorganisms is not considered to be fully enabled by the instant specification.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States

only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 2, 8-11, 13, 15-24 are rejected under 35 U.S.C. 102(e) as being anticipated by Short et al (Short et al US 6,057,103).

The independent claim 2 is drawn to a method of using host cells containing a vector expressing DNA from uncultivated microorgansims to detect a compound produced by the host cells. Claims 8 and 9 further limit the invention of claim 2 to a vector containing at least 20 kb or at least 50 kb of genomic DNA. Claim 10 –11 are drawn to the methods of claim 2 in which the uncultivated microorganisms include prokaryotic cells (claim 10) or prokaryotic cells of the Archaea domain (claim 11). Claim 13 is drawn to the method of claim 2 in which the samples of the uncultivated microorganisms are isolated from various sources in the environment. Claim 15 is drawn to the method of claim 2 in which the source of uncultivated microorganisms includes anaerobic cells. Claims 16-18 are directed to the method of claim 2 where the host cells contain a variegated population of vectors with different genomic DNA sequences with an average length of at least 20 kB and from at least 10 different species of microorganisms. Claims 19-21 are directed to a method of claim 2 in which the host cells are from a various bacterial species (claim 19), a species of Escherichia or Streptomyces (claim 20) or are *Escherichia coli* (claim 21). Claims 22-24 are drawn to the method of claim 2 in which the vector is a low-copy number, a single-copy number, a PAC or a BAC.

Short et al teach producing expression libraries of genomic DNA isolated from uncultivated microorganisms and detecting compounds produced by the microorganisms (column 4, lines 60-67 and columns 5-6). They teach the isolation of genomic DNA from uncultivated microorganisms by using an environmental sample from a marine environment. They contemplate the use of environmental samples from Artic or Antartic ice, water, volcanos and soil (columns 23 and 24, column column 7, lines 41-46 and column 8, lines 10-15). They also teach that the uncultivated microorganisms can include prokaryotic cells from Eubacterial and Archaebacterial domains including extremophiles (column 7, lines 1-10)

In addition, Short et al teach the use of low-copy number and single-copy number vectors such as fosmids, BAC vectors and PAC vectors, which are suitable for cloning large fragments of genomic DNA of about 40 kb to over 100 kb (column 6, lines 1-6, column 10, lines 23-31 and column 12 lines 14-29). They also teach transformation of host cells such as E. coli, Bacillus, and Streptomyces with replicable vectors containing the genomic DNA isolated from a large number of different microorganisms (column 8, lines 12-14, column 11, lines 49-50 and 58-67, column 12, lines 1-8 and column 5, lines 23-25). Thus, Short et al teach all that is recited by the instant claims.

Claims 2-8, 10, 13-22, 24-29, 30, 41-45 are rejected under 35 U.S.C. 102(e) as being anticipated by Thompson et al (Thompson et al US 5,824,485).
Claims 2, 8-11,13, 15, 16-22 and 24 have been described above. Claims 2-7 are drawn to a method of claim 2 in which the compound that is non-polymeric, non-proteinaceous, less than 7500 amu in molecular weight, a direct product of endogenous precursors of

the biosynthetic pathway and synthesized *de novo*. Claim 14 is drawn to the method of claim 2 in which the source of microorganisms includes prokaryotic cells with low G/C content genomes. Claims 25-30 are directed to the method of claim 2 in which the production of the compound is detected by its ability to induce a biological response from a test cell (claim 25), by various test cell responses (claim 26), by spectrometric methods (claim 27), by chromatographic methods (claim 28), by a cell-free assay (claim 29) or by its ability to induce a biological response from the host cell (claim 30). Claim 41 is drawn to a method for identifying a product of a biosynthetic pathway comprising cloning the DNA of uncultivated microorganisms into a vector, expressing the DNA in a host cell and detecting the product of the biosynthetic pathway. Claim 42 is drawn to a method for identifying a small molecule produced by a microorganism comprising expression of cloned genomic DNA from uncultivated microorganism in host cells and detection of a small molecule produced by the host cell. Claim 43 is drawn to a method of identifying a genetically engineered host cell which produces a small molecule by maintaining a host cell containing genomic DNA isolated from uncultivated microorganism under conditions to permit gene expression, detecting the production of the small molecule and identifying the host cell that produces the small molecule. Claims 44 and 45 are drawn to a method of producing and recovering a small molecule of interest by maintaining a host cell containing genomic DNA isolated from uncultivated microorganism under conditions to produce a small molecule.

Thompson et al teaches the production an expression library containing genomic DNA from environmental samples containing uncultivated microorganisms and

detection methods to isolate compound produced by host cells. They teach isolation of genomic DNA from uncultivated microorganisms including prokaryotes, prokaryotes with low G/C genome content and anaerobes from soil samples and suggest other sources such as marine sediments, water, and stressed environments (columns 13-17, 41, 42). They teach the cloning of the isolated genomic DNA into low-copy number vectors such as BACs or cosmids (column 19, lines 31-43), transformation of these vectors into host cells such as E. coli, bacillus and Streptomyces (column 18, lines 45-47) and the host cells containing vectors with inserts of genomic DNA of 30-42 kb in size from a plurality of microorganism species (column 25, lines 31-43 and column 46, lines 14-16). They teach the detection of compounds including those that are non-polymeric, non-proteinaceous, less than 7500 amu in molecular weight, direct products of the pathways and produced de novo by methods such as response from a test cell or the host cell, spectrometric detection or chromatographic detection (columns 24, 34 lines 26-30, 36 lines 14-20, 50 lines 33-39 and column 56). They further teach the isolation of specific compound producing clones and recovery of the compound (column 47). Thus, Thompson et al teach all that is recited in the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2, 10, 11,12 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Short et al in view of Fuerst et al (Frobisher & Fuerst Micorbiology Ch.2, pages 14-22, 1983) and Stein et al (J. Bacteriology, Vol. 178, pages 591-599, 1996). Claims 2, 10 ,11 and 14 have been described above. Claim 12 further limits the invention of claim 2 to the uncultivated micoroorganisms including Archaea domain cells from the group of Crenarachaeota, Euryarachaeota, and Karachaeota.

Short et al teach that the uncultivated microorganisms can contain prokaryotes from the Archaea domain, but do not specifically mention the phylogenetic groups with in this domain. Fuerst et al describes the phylogeny of the Archaeabacteria, including the methanogens and extreme halophiles (Euryarachaeota) and the thermoacidophiles (Crenarchaeota). Furthermore, Fuerst et al identifies the methanogens as strict anaerobes. In addition, Stein et al describes the cloning of genomic DNA from uncultivated prokaryotes known as Crenarchaeota into a fosmid to form an environmental DNA library (see abstract and page 592). It would have been obvious to

one of ordinary skill in the art to obtain genomic DNA from sources including specific phylogeny of Archaea domain cells such as Euryarachaeota and Crenarchaeota since these cells would be expected to contain a mixture of different undiscovered microorganism from which compounds could be isolated. One would have been motivated to do so in order to receive the expected benefit of increasing the possibility of discovering novel compounds from biosynthetic pathways. Absent of any evidence to the contrary, there would have been a reasonable expectation of success in using cells from Euryarachaeota and Crenarchaeota since they represent cells that can survive in stressed environments and may contain novel natural products.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tara L Garvey whose telephone number is (571) 272-2917. The examiner can normally be reached on Monday through Friday 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) (http://pair-direct.uspto.gov) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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Tara L Garvey
Examiner
Art Unit 1636

TLG

JAMES KETTER
PRIMARY EXAMINER